Parasellar xanthogranulomas

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OBJECT Xanthogranulomas are rare inflammatory masses most often found in the skin and eye. The incidence of intracranial xanthogranulomas is 1.6%–7%, with those found in the sellar and parasellar region being exceedingly rare and their etiology controversial. Sellar and parasellar xanthogranulomas are rarely reported in the western hemisphere, and their incidence in Western countries is unknown.

METHODS A prospectively acquired database of all endonasal endoscopic transsphenoidal surgeries performed at Weill Cornell Medical College was queried. Patients with histologically confirmed xanthogranulomas who were diagnosed and treated between 2003 and 2013 were included in the study. Patient history, demographic data, histological findings, and surgical approach were also evaluated.

RESULTS A total of 643 endonasal endoscopic procedures had been performed at the time of this study. Four patients (0.6%) were identified as having a histologically confirmed xanthogranuloma of the parasellar region, compared with an incidence of 6.7% for craniopharyngioma (CP) and 2% for Rathke cleft cyst (RCC). The most common symptom was visual loss, followed by headache. Preoperative diagnosis was CP in all cases. All patients underwent extended endonasal endoscopic transsphenoidal surgery with gross-total resection. Two patients developed panhypopituitarism after surgery. There were no CSF leaks. The mean follow-up was 61 months, at which time there were no recurrences. The key histological features differentiating xanthogranulomas from CPs were accumulation of foamy macrophages, multinucleated foreign body giant cells, cholesterol clefts, and hemosiderin deposits without stratified squamous epithelium. These histological features appear commonly as part of the spectrum of a secondary inflammatory response in an RCC.

CONCLUSIONS Parasellar xanthogranulomas most closely approximate CPs clinically but pathological evidence may suggest an RCC origin. Gross-total resection can be achieved through extended endonasal endoscopic transsphenoidal approaches, and is curative.

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KEY WORDS parasellar; xanthogranuloma; craniopharyngioma; Rathke cleft cyst; pituitary surgery

XANTHOGRANULOMAS are a rare and poorly understood pathological entity with only 1 other report published of a case arising in the western hemisphere.¹⁴ Miyajima et al., have reported the incidence of xanthogranulomas as 1.6%–7% based on autopsies. Xanthogranulomas are granulomatous reactions that consist of an accumulation of foamy macrophages, multinucleated foreign body giant cells, cholesterol clefts, hemosiderin deposits, necrotic debris, lymphocytic infiltrates, and fibrous proliferation.²¹ This is compared with Rathke cleft cyst (RCC), which consists of simple columnar or cuboi-

dal epithelium that is typically ciliated; and craniopharyngioma (CP), which can be either the adamantinomatous type with stratified squamous epithelium and wet keratin nodules, or the papillary type with squamous epithelium that forms papillae without calcification or keratin nodules.²⁷ The etiology of xanthogranulomas in the sellar region is controversial, with 2 hypotheses frequently described. The first theory is that xanthogranulomas arise after an inflammatory reaction, hemorrhage, and destruction of an RCC. The other theory states that these lesions arise from a secondary inflammatory progression of a CP.^{1,3,20}

ABBREVIATIONS CP = craniopharyngioma; GTR = gross-total resection; RCC = Rathke cleft cyst.

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Radiological and immunohistochemical investigations by themselves are not sufficient to definitively diagnose xanthogranulomas.^{1,14} These lesions have been described to occur on a spectrum of transitional states from benign RCC to neoplastic CPs.²⁷

We report on the clinical and pathological findings in 4 documented patients with xanthogranulomas in the sellar region and the incidence of such lesions in the western hemisphere. Since diagnosis is heavily dependent on histological findings, proper resection and sufficient diagnostic tissue is critical to provide an accurate diagnosis. No prior cases have been treated with an endonasal endoscopic approach. In this report we discuss 4 cases managed using this approach, in which the patients were surgically cured, and discuss the histological diagnosis, incidence, and etiology of this rare and unusual lesion.

Methods

We queried a prospectively acquired database of a consecutive series of endonasal, endoscopic surgeries performed at Weill Cornell Medical College by the senior author (T.H.S.) between 2003 and 2013. Cases in which a xanthogranuloma was recorded in the pathology report were reviewed by the neuropathologist to confirm the diagnosis. The demographic data, histological findings, operative reports, office record, and hospital notes were reviewed and patients were called to obtain the most recent follow-up.

Results

Over a 10-year period, 643 endonasal endoscopic procedures were performed in the sellar and parasellar area. Four (0.6%) were for xanthogranulomas, 43 (6.7%) were for CPs, and 13 (2%) were for RCCs.

Case Reports

Case 1

A 15-year-old girl with a history of Type I diabetes mellitus presented with intractable headaches and was found to have a suprasellar mass on contrast-enhanced MRI scans. Her preoperative MRI suggested a CP with the presence of hemorrhagic or proteinaceous intracystic contents (Table 1). An extended endoscopic transsphenoidal, transsellar, transplanum, transtuberculum approach was performed. Intraoperatively, a mass with yellow crystalline fluid was found and gross-total resection (GTR) was achieved. Pathological findings were consistent with a xanthogranuloma. No immediate postoperative complications were noted and postoperative imaging confirmed GTR.

Follow-up at 115 months revealed that the patient had developed polyglandular autoimmune syndrome. In addition to the diabetes mellitus, Hashimoto thyroiditis and celiac disease were diagnosed in this patient several years after the procedure. The patient currently suffers from complications of these diseases, including hypophagia.

Case 2

A 66-year-old woman presented with a 4-year history

of progressive visual loss. The workup included visual field testing, which showed bitemporal hemianopia, and an MRI scan (Table 1). The scan was consistent with either an RCC or CP with proteinaceous or hemorrhagic debris. An extended endonasal transsphenoidal, transsellar, transplanum, transtuberculum approach was performed.

Pathological investigation showed a cyst lined with cuboidal, columnar, and stratified squamous epithelium. The cyst wall was fibrotically thickened, with chronic granulomatous inflammatory cell infiltrates, hemosiderin-laden macrophages, and cholesterol clefts with foreign body-type giant cells. The cyst contained hemorrhage and amorphous debris. Histological investigation also showed a small (1.5-cm) nested proliferation of round-to-polyhedral cells with vacuolated granular cytoplasm situated in a perivascular distribution. Based on results of immunohistochemistry tests, these cells were strongly positive for chromogranin and negative for S100, A103, and cytokeratin. These findings were best interpreted as paraganglionic tissue from the sinonasal tract. Thus a diagnosis of benign cyst lining with xanthogranulomatous reaction was made.

Pituitary function test results were normal postoperatively and imaging confirmed GTR. There were no immediate postoperative complications and the patient's vision markedly improved (Table 1). Follow-up at 90 months revealed stable vision and no endocrinopathies.

Case 3

A 42-year-old woman complained of a 2-week history of visual loss in her left eye (Table 1, Fig. 1). Preoperative MRI results were consistent with a diagnosis of CP. An extended endonasal endoscopic transsphenoidal, transsellar, transplanum, transtuberculum approach was performed. The stalk was anatomically preserved but the tumor was clearly infiltrating and arising from the stalk.

Pathological findings were consistent with a xanthogranuloma with cholesterol clefts, foamy histiocytes, hemosiderin deposits, calcifications, a lymphocytic infiltrate, and occasional multinucleated giant cells. Postoperatively, the patient had panhypopituitarism and diabetes insipidus. The patient's postoperative imaging confirmed GTR (Fig. 1).

Long-term follow-up for this patient was 54 months, at which point she was noted to be asymptomatic. At follow-up, the patient had low normal triiodothyronine, but did not require any endocrine-related medications. She reports no problems with her vision (Table 1).

Case 4

A 49-year-old woman was found to have an asymptomatic intradural anterior skull base neoplasm (Fig. 2, Table 1). She underwent an extended endonasal endoscopic transsphenoidal, transsellar, transplanum, transtuberculum surgery. Intraoperatively, gross infiltration of the pituitary stalk was seen and was resected for GTR.

The histological specimen consisted of fragments of fibrovascular tissue with prominent cholesterol clefts, hemosiderin deposition, and giant cell granulomatous reaction. There was no evidence of squamous epithelium or histological features of CP. These findings were consistent

TABLE 1. Preoperative and postoperative clinical findings in 4 patients with sellar xanthogranulomas*

Age (yrs), Sex	Endocrine Function		Visual Function		Imaging Results	Postop CSF Leak
	Preop	Postop	Preop	Postop		
15, F	↓IGF-I; all others normal	All others normal	Lt, inf temporal field deficits	Normal	Suprasellar; >1 cm diameter	No
66, F	All normal	↑PRL but asymp; all others normal	Bitemporal hemianopia	Normal	Suprasellar; >1 cm diameter	No
42, F	All normal	↓FT3; ↓T ₃	Bitemporal hemianopia	Normal	Sellar/suprasellar; 2.1 × 1.5 × 1.4 cm	No
49, F	↓Testosterone; ↓LH; ↑PRL; all others normal	↓T ₃ ; ↓T ₄ ; ↓FT4; ↓cortisol	Normal	Normal	Sellar/suprasellar; 1.7 × 1.5 × 1.1 cm	No

Asymp = asymptomatic; FT3 = free triiodothyronine; FT4 = free thyroxine; IGF-I = insulin-like growth factor-I; inf = inferior; LH = luteinizing hormone; PRL = prolactin; T₃ = triiodothyronine; T₄ = thyroxine.

* All 3 patients with abnormal vision had improvement postsurgery. These same patients remained intact or quickly returned to full endocrine function. None of the patients had postoperative imaging findings indicative of residual mass and none reported a CSF leak.

with a xanthogranuloma of the parasellar region. Postoperative MRI confirmed radiographic GTR (Fig. 2).

The patient had maintained normal visual function and had panhypopituitarism at 6-month follow-up.

Discussion

Cases of xanthogranulomas in the sellar region have been reported in the Asian literature, but only 1 prior report exists in the English-language literature (Table 2).^{1,2,14–16,20,25,26} Hence, the incidence of xanthogranulomas in Western countries is unclear. Likewise, the management of these lesions has been almost universally through craniotomy or microscopic transsphenoidal surgery.^{1,12,20} The endonasal endoscopic approach lends itself to the management of these lesions because the exposure and visualization of the supra- and parasellar areas is generally superior to a microscopic transsphenoidal approach, while being less invasive than a craniotomy.

Currently, xanthogranulomas are histologically diagnosed by an accumulation of foamy macrophages, multinucleated foreign body giant cells, cholesterol clefts, lymphocytic infiltration, hemosiderin deposits, and fibrous proliferation (Fig. 3).^{20,21} Paulus et al. proposed this pathological pattern and compared these lesions to CPs. They found a predilection for occurrence at a younger age, a higher likelihood of the mass being intrasellar, more severe endocrine deficits, and less visual involvement. Our 4 patients had a median age of 43 years at the time of operation and had predominantly suprasellar masses. Two

of 4 had mild endocrine involvement and 3 of 4 had visual manifestations. Operation was curative for all 4 patients.

These lesions are difficult to diagnose clinically because on imaging they mimic CPs, and they present with varying levels of intensity on MRI due to the unpredictable pattern of hemorrhage and calcification in the lesion.^{1,12,21} Operatively these lesions also mimic CPs due to the well-described finding of the “machine oil” consistency of CP.^{1,12,21} Many authors have described the presentation of endocrine, visual, and neurological manifestations in parasellar xanthogranulomatous reactions, but a unique symptomatology has not yet been elucidated.^{1,2,6–8,12,15,16,20,21,23,25–27}

Furthermore, there is significant controversy regarding the etiology and development of these unusual lesions. One theory of the etiology of these parasellar lesions is that all xanthogranulomas arise from inflammatory processes occurring in preexisting CPs.³ A CP is classically described as one of two types; squamous-papillary and adamantinomatous.²¹ The squamous-papillary type has epithelium with papillary projections into the surrounding tissue, most represented by the structure of the oral mucosa.⁵ Histological descriptions of adamantinomatous CPs have detailed stratified squamous-type epithelium with wet, sheaf-like keratin nodules resembling the calcifying odontogenic cysts of the jaw or tooth bud (Fig. 4).^{10,22,27} The presence of squamous epithelium in xanthogranulomas as well as the presence of rare calcifications

FIG. 1. Case 3. **Left:** Preoperative sagittal MRI study obtained with Gd showing a large homogeneously enhancing suprasellar mass. **Right:** Postoperative sagittal T1-weighted MRI study obtained without contrast showing fat graft in the location of resected tumor.

FIG. 2. Case 4. **Left:** Preoperative sagittal MRI study obtained with Gd showing a suprasellar mass. **Right:** Postoperative MRI study obtained with Gd showing complete resection of the mass and an enhancing nasoseptal flap in the sphenoid sinus.

TABLE 2. Literature review of reported cases of pituitary lesions with xanthogranulomatous features*

Authors & Year	No. of Patients	Findings	Surgical Approach	Country of Origin
Kurisaka et al., 1998	1	Xanthogranuloma w/ ciliated columnar epithelium	Transsphenoidal	Japan
Hama et al., 1999	1	Lymphocytes, neutrophils, foamy cells, fibrosis, ciliated columnar epithelium	Transsphenoidal	Japan
Nakasu et al., 1999	1	Xanthogranuloma w/ columnar epithelial cells	Transsphenoidal	Japan
Paulus et al., 1999	37	Xanthogranulomas—3/37 adamantinomatous epithelium, 13/37 squamous to ciliated cuboidal epithelium	Transsphenoidal	Germany
Flanagan et al., 2002	3	Foreign body giant cells, cholesterol clefts, cystic cuboidal epithelium	Transsphenoidal (2); pterional (1)	UK
Reithmeier et al., 2002	1	Foam cells, Touton-like giant cells, histiocytes, fibrotic tissue	Transsphenoidal	Germany
Burt et al., 2003	2	Foamy histiocytes, lymphocytes, cholesterol clefts, multinucleated giant cells	Transsphenoidal (1); frontal craniotomy (1)	Australia
Yonezawa et al., 2003	1	Cholesterol clefts, multinucleated giant cells, focal hemorrhage, fibrous tissue, no epithelium	Transsphenoidal	Japan
Jung et al., 2006	2	Xanthogranulomas w/ cuboidal epithelium & ciliated cuboidal to squamous epithelium	Transnasal-transsphenoidal	Germany
Le et al., 2007	20	2/20 xanthogranulomas w/ no epithelium, 13/20 xanthogranulomatous change to RCC, 5/20 xanthogranulomatous change to CP	Not reported†	US
Liu et al., 2008	1	Xanthogranuloma w/ necrosis & calcification	Transcranial	Taiwan
Sugata et al., 2009	1	Xanthogranuloma w/ fibrous tissue, no epithelium	Interhemispheric	Japan
Arai et al., 2010	1	Xanthogranuloma w/ no epithelium	Endonasal transsphenoidal	Japan
Kamoshima et al., 2011	5	Xanthogranulomas w/ calcification & monocytes—2/5 nonkeratinized epithelium, 3/5 no epithelium	Transsphenoidal (4); transcranial (1)	Japan
Miyajima et al., 2011	1	Cholesterol clefts, hemosiderosis, macrophages, fibrous connective tissue	Pterional	Japan
Nishiuchi et al., 2012	1	Small epithelial cells, foamy macrophages, lymphoid infiltration, necrosis, hemosiderin deposits	Transsphenoidal	Japan
Amano et al., 2013	7	Cholesterol cleft granulomas, hemosiderin deposits, chronic inflammation infiltrates, 6/7 multinucleated giant cells, 5/7 calcification, 6/7 RCC components, 1/7 ossified mass	Endonasal transsphenoidal microsurgery	Japan
Present study	4	Xanthogranulomas—2/4 RCC components, 2/4 no epithelium	Endonasal endoscopic transsphenoidal	US

UK = United Kingdom.

* Data include all described xanthogranulomatous changes in the parasellar region in the literature. The term “xanthogranuloma” is used when macrophages, multinucleated giant cells, cholesterol clefts, and hemosiderin deposits were specifically reported. Epithelium type not included unless specifically reported in the case study.

† Histological study; surgical approaches were not reported.

have driven the theory that xanthogranulomas of the sellar region arise from adamantinomatous CPs (Fig. 5).²¹

Some case reports have instead shown that xanthogranulomas have RCC structures. The histological features most commonly seen in RCCs include columnar and cuboidal cystic cells with varying degrees of ciliation, and goblet cells.^{21,27} Le et al. described 28 cases of RCC, 13 of which had prominent xanthomatous reaction. Two of our 4 cases had some cystic features and thus were probably a secondary progression from RCCs by this explanation. The other 2 appeared to be xanthogranulomas without any epithelium. This however could have been simply from submission of an incomplete survey of the lesion to the pathology laboratory.

In 2013, Prieto and Pascual published an article postulating that there is a link between the Rathke pouch, squamous-papillary CPs, and adamantinomatous CPs.²² They show support for adamantinomatous CPs arising

from the remnant epithelium of the Rathke pouch, based on the topographical distribution of epithelial cells during development of the infundibulo-tuberal region and the suprasellar-infrachiasmatic region. Since these lesions are embryonic in nature, they are more likely to be present in younger patients and at these 2 sites. If inflammation persists, then it can be expected to display some features representative of adamantinomatous CP at these locations. Squamous-papillary CPs on the other hand are more likely to result from the metaplasia of adenohypophysial cells in the pituitary gland, and may tend to arise at the ventricular floor or intraventricularly.

Folkerth et al.⁸ and Deodhare et al.⁶ described patients with xanthomatous hypophysitis. Their histological findings showed foamy histiocytes and lymphocytes within a matrix of anterior pituitary acinar cells and intact vasculature. There was a distinct and marked lack of cystic cell components and squamous cells, as well as compo-

FIG. 3. Photomicrograph showing a specimen obtained in a case of pure xanthogranuloma. Note cholesterol clefts (seen as empty areas), multinucleated giant cells, foamy macrophages, and lymphoplasmacytic infiltration. There is a marked absence of structured epithelium of either cuboidal or squamous type. H & E, original magnification $\times 100$. Figure is available in color online only.

nents of a xanthogranuloma such as giant cells, hemosiderin deposits, cholesterol clefts, and fibrous tissue. It is likely that these represent a primary xanthomatous reaction rather than a reaction to a squamous-papillary CP or RCC. Nishikawa et al.¹⁹ described xanthomatous hypophysitis caused by an RCC. They found ciliated columnar cells, foamy cells, and lymphoid cells in the anterior and posterior pituitary, and fibrosis in the adenohypophysis. Meanwhile, Roncaroli et al.²⁴ reported a granulomatous hypophysitis caused by a ruptured RCC. They found that the anterior pituitary gland was entirely altered by noncaseous giant cell granulomas that contained eosinophilic amorphous material, calcium deposits, mature lymphocytes, plasma cells, and neutrophils.

FIG. 4. Photomicrograph showing an example of a pure CP of the adamantinomatous type. There are areas of stratifying squamous epithelium with a consistent adamantinomatous basaloid layer of cells. Loose areas with cystic cavities appear heterogeneously throughout. Also note a keratin nodule formation occurring in a sheaf-like arrangement. H & E, original magnification $\times 100$. Figure is available in color online only.

FIG. 5. Photomicrograph showing a specimen obtained in a case of xanthogranulomatous reaction to a CP. Some of the typical features of the xanthogranuloma are seen, including foamy macrophages, a smaller cholesterol cleft, multinucleated giant cell, and a lymphocytic presence. Also noted are the typical features of an adamantinomatous CP, including squamous-like epithelium, keratin, and loose structural areas. H & E, original magnification $\times 200$. Figure is available in color online only.

In addition to these findings, Le et al.¹⁴ described the occurrence of squamous metaplasia in nearly 40% of their resected RCCs. They showed a high occurrence of xanthomatous change (69%) in these samples, which may suggest part of the process of secondary inflammation that occurs in RCCs. In our review of the literature, 29 of the 72 described cases of xanthogranulomatous change in the parasellar region had some form of epithelium consistent with RCC, 2 of 72 had squamous epithelium, and 3 had adamantinomatous-type epithelium. The remaining samples either had no epithelium or it was not described in the report. Paulus et al.²¹ originally suggested the idea that the squamous epithelium that is rarely seen in xanthogranulomas may indeed be due to a metaplastic process, and this is supported by Le et al.'s report.

These findings do not definitely conclude that histogenesis of xanthogranulomas occurs in the sellar region; however, with the body of evidence that is accumulating for these lesions, it appears more than ever that they arise secondarily from an inflammatory reaction to an RCC, contrary to their clinical mimicry of CPs.

The spectrum of inflammatory change in xanthomatous reactions is varied and difficult to distinguish; thus, a thorough sampling of the entire mass is still critical for histological examination. Failure to fully sample the mass histologically can misleadingly show a pure xanthogranuloma, whereas in actuality there may be a reaction to a different primary lesion. Such diligence is important to prevent the misdiagnosis of a xanthogranuloma as an inflammatory reaction to an RCC or CP. Finally, since the embryological origins of the cells of the lesion may play a role, the age of the patient and location of the lesion should also be noted because it may help further the understanding of the pathogenesis.

Conclusions

Xanthogranulomas represent roughly 0.6% of parasel-

lar tumors in the western hemisphere. Until a more definitive method of diagnosing xanthogranulomas in the sellar region is developed, neurosurgeons must be cognizant of their existence, especially when dealing with the resection of an RCC or a CP. Evidence is accumulating favoring an RCC origin of these lesions but is not conclusive yet, and for this reason extra care must be taken to submit a proper survey of the mass to ensure an accurate diagnosis. The endonasal endoscopic approach is currently the least invasive definitive method for achieving surgical cure.

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